The amendments and new claims find support throughout the application including the Drawings and claims as filed originally.

Particular support for "heteropolymeric" in claims 1, 52, 54, 57, 62, 64, and 68 can be found on pg. 9, line 15 to pg. 11, line 27 (disclosing a variety of peptide polymers having more than one amino acid type ie., heteropolymeric peptide sequences). Specific examples of heteropolymeric sequences include enkephalin, Leu-enkephalin, vasopressin, and endolthelin. See also claim 24 as filed originally.

Claims 1, 52, 54, 64, and 68 were amended to further specify the stabilizing peptide "Z" as having at least two identical amino acid units. Specific support for that language can be found at pg. 18, lines 26-30 (disclosing "Z" with at least two Lys residues). Further support can be found at pgs. 15-16, bridging paragraph and pg. 16, lines 21-32. See also pg. 19, line 16 to pg. 21, line 9 (disclosing peptide conjugates with particular Z peptides having at least two identical amino acid residues). See also claim 1 as filed originally.

Claim 24 has been amended to improve claim dependency. Specifically, the claim has been amended to depend from claims 1 and 10.

Claim 29 was amended at the suggestion of the Examiner.

Particular support for the amendment to claim 62 can be found at pg. 17, lines 19-22 (providing for Z as $(Dbu)_n$ or $(Dbr)_n$).

New claim 69 has been written along lines of claim 3 (now canceled) so that stabilizing peptide "Z" is covalently bonded to the N terminus of the X peptide. Specific support for the claim can be found on pg. 18, first full paragraph. Examples of such peptide conjugates in which Z is so bound can be found at pg. 19, lines 25-27; pg. 20, lines 8-11 and 26; pg. 20, and lines 30-31. See also claim 1 as filed originally.

Specific support for new claims 70 and 71 are found on pgs. 17-18, bridging paragraph.

Canceled claim 4 has been re-written as new claim 72.

No new matter has been added by virtue of the claim amendments or new claims.

Turing to the office action, Applicants gratefully acknowledge withdrawal of the rejection based on Larsen (WO 98/11126).

On pgs. 2-3 of the Action, the position was taken that a substitute specification must be submitted for a new sequence listing. At pg. 4, the Examiner stated that the requirement would be reconsidered if the phrase "a truncated fragment thereof" was deleted. Although Applicants respectfully disagree that deletion of the phrase is required, the phrase has been deleted from claim 68 solely to further prosecution. Related language has been cancelled from claim 24. Deletion of the phrases from claims 24 and 68 is not intended, nor should it be construed as, a surrender of any subject matter or related to claim patentability.

Not true

Accordingly, reconsideration and withdrawal of the request to provide another substitute specification and sequence listing are earnestly requested.

Claim 37 stands rejected under 35 USC §112, first paragraph. Although Applicants respectfully disagree with the basis for the rejection, grounds for it have been addressed by this submission.

Claims 1-32, 37 and 52-68 stand rejected under 35 USC §112, second paragraph, on various grounds. Action at pgs. 6-7. Each rejection is addressed in the order in which it appears in the Office Action.

Claim 1 stands rejected for reciting the word "about". Applicants must respectfully disagree as follows.

As an initial matter, use of "about"or "at least about" is not inherently indefinite. MPEP 2173.05(b), part A. According to the USPTO, "at least about" is indefinite when: 1) there is close prior art, and 2) there is nothing in the specification, prosecution history, or the prior art to provide any indication as to what range of specific activity is covered by the term "about". MPEP 2173.05(b)A (discussing *Amgen , Inc. v. Chugai Pharmaceutical* Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)).

Respectfully, the Office has failed to meet this two-step test. Specifically, no "close" prior art has been identified in the §112, second paragraph, rejection. Also, Applicants' specification provides ample indication of the range of activity intended. For example, see pg. 5, lines 8-34 of the application (reproduced in part as follows, emphasis added):

> leucine aminopeptidase in about 50mM phosphate buffer solution at about pH 7.4 at about 37C or in plasma or in serum is **at least about 2, preferably at least about 3, such as at least about 5,, more preferably at least about 7, such as at least about 9, eg., at least about 10**...

In view thereof, there is no basis for maintaining the indefiniteness rejection for recitation of the phrase "at least about". Reconsideration and withdrawal of the rejection are requested.

Claim 1 was rejected for reciting the phrase "e.g., 2, 4-diaminobutanoic acid and 2,3-diamainopropanoic acid". Action at pg. 6. The rejection has been addressed by this submission.

Claim 1 stands rejected for reciting the phrase "covalently bound". Action at pg. 6. Although Applicants respectfully disagree that the phrase is indefinite, the Examiner's suggested phrase "covalently bonded" has been adopted.

Claims 3, 4, and 5 have been cancelled.

Claim 29 stands rejected as being indefinite as to the process steps. Solely to further prosecution of the claim, language suggested by the Examiner has been adopted in step b) of the claimed method. Applicants respectfully disagree that amended claim 29 is indefinite particularly when read in light of the specification.

For example, pg. 32, line 1 to pg. 37, last line of the specification, discloses methods for producing the peptide conjugate of claim 1. Specifically disclosed are preparation strategies employing conventional recombinant DNA technology, techniques for isolating and cloning the recited nucleic acid sequence, making vector from the nucleic acid, and association with appropriate promoter sequence. Specification at pg. 32, lines 1-last line. Further disclosed are a variety of suitable promoter, terminator, polyadenylation, and replication sequences, at pg. 33, line 10 to pg. 35, line 4. Particular methods of introducing nucleic acid expression vectors are provided eg., at pg. 35, line 26 to pg. 36, line 5. Illustrative host cells are provided at pg. 36, line 7 to pg. 37, last line.

Accordingly, one of skill having read the disclosure would not find amended claim 29 indefinite. Withdrawal of the rejection is requested.

Claim 19 was rejected as being indefinite on grounds that "Xaa" is undefined in many of the sequences. Action at pg. 7. Applicants respectfully disagree.

Claim 19 recites that "each of Xaa is independently selected from the group consisting of Ala, Leu, Ser, Thr, Asn, Gln, Asp, Glu, Arg, His, Med, Orn and the amino acids of Formula I ..." (see claim 19). Since Xaa is specifically defined by reference to a chemical structure, there can be no basis for the assertion that the claim is indefinite. Reconsideration and withdrawal of the rejection are requested.

Claims 54 and 62 stand rejected on stated grounds. Bases for each rejection has been addressed in this submission. Specifically, the claims have been amended.

In view thereof, reconsideration and withdrawal of the rejections under 35 USC §112, second paragraph, are earnestly requested.

Claims 1-2, 19, 24, 52-57, 62 and 64-68 stand rejected as being anticipated under 35 USC §102(b) in view of Neer. Although Applicants respectfully disagree with the rejection as formulated, grounds for it have been addressed by this submission.

In particular, each of claims 1, 52, 54, 57, 62, 64, and 68 has been amended to recite a Z sequence having **at least two identical amino acid** units. In contrast, the cited, "Z" sequence from **Neer has no identical amino acids** ie., the sequence "KLQDVHNF" consists of different amino acid units. Accordingly, there can be no anticipation of the claimed invention.

Applicants respectfully traverse the rejection as to claims 66-67 (methods of neuron inhibition). Neer, as cited, does not disclose a method for inhibiting neurons. Thus, there can be no anticipation and the rejection should be withdrawn.

In view thereof, reconsideration and withdrawal of the §102 rejection are earnestly requested.

Claim 5 stands rejected under 35 USC §102(b) as being anticipated by Katz or Ryser. Although Applicants respectfully disagree with the rejection, basis for it has been addressed by this submission. The claim has been canceled.

Remaining basis for rejecting claims 1-2, 19, 24, 52-57, 62 and 64-68 under 35 USC §102(b) are addressed together in the interest of brevity. Although Applicants respectfully disagree with each position taken, bases for the rejections are addressed herein.

Specifically, claims 1, 52, 54, 57, 62, 64 and 68 have been amended to recite a **heteropolymeric** X sequence ie., a peptide sequence with different amino acid unit types. In contrast, the cited references are alleged to disclose polylysine (Katz, Ryser, Doherty, and

Burger) or polyarginine (Sumner-Smith). Unlike the heteropolymeric X sequence of the claims, the cited sequences are understood to be **homopolymers**. That is, polylysine and polyarginine consist of reiterations of the same amino acid unit (Lys or Arg). Since heteropolymers and homopolymers are distinct, there can be no anticipation of the claimed invention.

Applicants respectfully traverse the rejection as to claims 66-67 (methods of neuron inhibition). None of the Katz, Ryser, Doherty, and Burger or Sumner-Smith references, as relied on, disclose a method for inhibiting neurons. Thus, there can be no anticipation and the rejection should be withdrawn.

In view thereof, it is submitted that bases for the outstanding §102(b) rejections have been addressed.

Attached to this submission is a marked-up version of the changes made to the specification and/or claims. The attached page is captioned "version with markings to show changes made".

It is believed that the application is in condition for allowance, which action is earnestly solicited. Although it is not believed that any fee is needed to consider this submission, the USPTO is authorized to charge our deposit account no. **04-1105** should such fee be deemed necessary.

Respectfully submitted,

Date: 4 JANUARY 2002 By: _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1, 24, 29, 52, 54, 57, 62, 64 and 68 have been amended as follows:

1. (Amended) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence, of 4-20 amino acid units covalently [bound] bonded by its N terminus to the C terminus end of X wherein each amino acid unit in said stabilising peptide sequence, Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring [, e.g., 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid]; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence, X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at

about pH 7.4 at about 37°C or in serum or plasma is at least about 2; or a salt thereof, wherein Z comprises at least two identical amino acid units.

24. (Amended) The peptide conjugate according to claim [16] 1 or 10, wherein X is selected from the group consisting of enkephalin, Leu-enkephalin, Met-enkephalin, angioten-sin I, angioten-sin II, vasopressin, endothelin, vasoactive intestinal peptide, neurotensin, endorphins, insulin, gramicidin, para-celsin, delta-sleep inducing peptide, gonadotropin-Releasing hormone, human parathyroid hormone (1-34), [truncated erythropoietin analogues, specifically] EMP-1, Atrial natriuretic peptide (ANP, ANF), human brain natriuretic peptide (hBNP), cecropin, kinetensin, neurophysins, elafin, guamerin, atriopeptin I, atriopeptin II, atriopeptin III, deltorphin I, deltorphin II, vasotocin, bradykinin, dynorphin, dynorphin A, dynorphin B, growth hormone release factor, growth hormone, growth hormone releasing peptide, oxytocin, calcitonin, calcitonin gene-related peptide, calcitonin gene-related peptide II, growth hormone releasing peptide, tachykinin, adrenocorticotropic hormone (ACTH), brain natriuretic polypeptide, cholecystokinin, corticotropin releasing factor, diazepam binding inhibitor fragment, FMRF-amide, galanin, gastric releasing polypeptide, gastric inhibitory polypeptide, gastrin, gastrin releasing peptide, glucagon, glucagon-like peptide-1, glucagon-like peptide-2, LHRH, melanin concentrating hormone, melanocyte stimulating hormone (MSH), alpha-MSH, morphine modulating peptides, motilin, neurokinin A, neurokinin B, neuromedin B, neuromedin C, neuromedin K, neuromedin N, neuromedin U, neuropeptide K, neuropeptide Y, pituitary adenylate cyclase activating polypeptide (PACAP), pancreatic polypeptide, peptide YY, peptide histidine-methionine amide (PHM), secretin, somatostatin, substance K, thyrotropin-releasing hormone (TRH), kyotorphin, melanostatin (MIF-1), thrombopoeitin analogs, in particular AF 12505 (Ile-Glu-Gly-Pro-Thr-Leu-Arg-Gln-Trp-Leu-Ala-Ala-Arg-Ala) (SEQ ID NO. 14), insulin-like growth factor I (57-70) (Ala-Leu-Leu-Glu-Thr-Tyr-Cys-Ala-Thr-Pro-Ala-Lys-Ser-Glu) (SEQ ID NO. 15), insulin-like growth factor I (30-41) (Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO. 16), insulin-like growth factor I (24-41)(Tyr-Phe-Asn-Lys-Pro-Thr-Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO. 17) , insulin-like growth factor II (33-40) (Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO. 18), insulin-like growth factor II (33-40) (Tyr-Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO. 19), insulin-like growth

factor II (69-84) (Asp-Val-Ser-Thr-Pro-Pro-Thr-Val-Leu-Pro-Asp-Asn-Phe-Pro- Arg-Tyr) (SEQ ID NO. 20), growth hormone (GH)-releasing peptide-6 (GHRP-6) (His-DTrp-Ala-Trp-DPhe-Lys-NH2) (SEQ ID NO. 21), beta-Interleukin I (163-171) (Val-Gln-Gly-Glu-Glu-Ser-Asn-Asp-Lys) (SEQ ID NO. 22), beta-Interleukin II (44-56) (Ile-Leu-Asn-Gly-Ile-Asn-Asn-Tyr-Lys-Asn-Pro-Lys-Leu) (SEQ ID NO. 23), Interleukin II (60-70) (Leu-Thr-Phe-Lys-Phe-Tyr-Met-Pro-Lys-Lys-Ala) (SEQ ID NO. 24), exendin-4 (GLP-1 analog) (His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2) (SEQ ID NO. 25), exendin-3 (GLP-1 analog) (His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser) (SEQ ID NO. 26), epidermal growth factor (20-31) Cys(Acm)-Met-His-Ile-Glu-Ser-Leu-Asp-Ser-Tyr-Thr-Cys(Acm) (SEQ ID NO. 27), bivalirudin (Hirulog) (D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu) (SEQ ID NO. 28), hirulog-1 D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Tyr-Leu (SEQ ID NO. 29), C-type natriuretic peptide (1-53) (CNP) (Asp-Leu-Arg-Val-Asp-Thr-Lys-Ser-Arg-Ala-Ala-Trp-Ala-Arg-Leu-Leu-Gln-Glu-His-Pro-Asn-Ala-Arg-Lys-Tyr-Lys-Gly-Ala-Asn-Lys-Lys-Gly-Leu-Ser-Lys-Gly-Cys-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Gly-Ser-Met-Ser-Gly-Leu-Gly-Cys; Disulfide bridge: Cys37-Cys53) (SEQ ID NO. 30), "Mini ANP" (Met-Cys-His-cyclohexylAla-Gly-Gly-Arg-Met-Asp-Arg-Ile-Ser-Cys-Tyr-Arg, disulfide bridge cys2-cys13) (SEQ ID NO. 31), Melanotan-II (also known as MT-II, alpha-MSH4-10-NH2, or Ac-Nle4-Asp5-His6-D-Phe7-Arg8-Trp9-Lys10) (SEQ ID NO. 32), thymosin alpha1 (TA1) (Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn) (SEQ ID NO. 33), ornipressin (also known as 8-ornithine-vasopressin, (POR-8), vasopressin), Cys-Phe-Ile-Gln-Asn-Cys-Pro-Orn-Gly-NH2, Disulfide bridge: Cys1-Cys6) (SEQ ID NO. 34), octreotide (201-995) (DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol; disulfide bridge: Cys2-Cys7) (SEQ ID NO. 35), eptifibatide (INTEGRILIN), calcitonin gene-related peptide (CGRP) (Ala-Cys-Asp-Thr-Ala-Thr-Cys-Val-Thr-His-Arg-Leu-Ala-Gly-Leu-Leu-Ser-Arg-Ser-Gly-Gly-Val-Val-Lys-Asn-Asn-Phe-Val-Pro-Thr-Asn-Val-Gly-Ser-Lys-Ala-Phe-NH_2; Disulfide bridge: Cys2-Cys7) (SEQ ID NO. 36), endomorphin-1 Tyr-Pro-Trp-Phe-NH2 (SEQ ID NO. 37); endomorphin-2 Tyr-Pro-Phe-Phe-NH_2 (SEQ ID NO. 38), nociceptin (also known as Orphanin FQ, Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-

Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln) (SEQ ID NO. 39), angiotensinogen (1-13) (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His) (SEQ ID NO. 40), adrenomodullin (1-12) (Tyr-Arg-Gln-Ser-Met-Asn-Asn-Phe-Gln-Gly-Leu-Arg) (SEQ ID NO. 41), antiarrhytmic peptide (AAP) (Gly-Pro-Hyp-Gly-Ala-Gly) (SEQ ID NO. 42), Antagonist G (Arg-DTrp-(nMe)Phe-DTrp-Leu-Met-NH_2), indolicidin (Ile-Leu-Pro-Trp-Lys-Trp-Pro-Trp-Trp-Pro-Trp-Arg-Arg-NH_2) (SEQ ID NO. 43), osteocalcin (37-49) (Gly-Phe-Gln-Glu-Ala-Tyr-Arg-Arg-Phe-Tyr-Gly-Pro-Val) (SEQ ID NO. 44), cortistatin 29 (1-13) (Glp)-Glu-Arg-Pro-Pro-Leu-Gln-Gln-Pro-Pro-His-Arg-Asp) (SEQ ID NO. 45), cortistatin 14 Pro-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Ser-Ser-Cys-Lys; Disulfide bridge: Cys2-Cys13 (SEQ ID NO. 46), PD-145065 (Ac-D-Bhg-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO. 47), PD-142893 (Ac-D-Dip-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO. 48), fibrinogen binding inhibitor peptide (His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val) (SEQ ID NO. 49), leptin (93-105) (Asn-Val-Ile-Gln-Ile-Ser-Asn-Asp-Leu-Glu-Asn-Leu-Arg) (SEQ ID NO. 50), GR 83074 (Boc-Arg-Ala-DTrp-Phe-DPro-Pro-Nle-NH_2) (SEQ ID NO. 51) Tyr-W-MIF-1 (Tyr-Pro-Trp-Gly-NH_2) (SEQ ID NO. 52), parathyroid hormone related peptide (107-111) (Thr-Arg-Ser-Ala-Trp) (SEQ ID NO. 53), angiotensinogen (1-14) Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn (SEQ ID NO. 54), Leupeptin (Ac-Leu-Leu-Arg-CHO), sandostatin and any modified [or truncated] analogue thereof.

29. (Amended) A method for producing the peptide conjugate of claim 1, comprising

d) introducing a nucleic acid sequence encoding said conjugate into a host cell;
e) culturing said host cell <u>for a time</u> and <u>under conditions effective to produce said peptide conjugate, and</u>
f) isolating said conjugate from the culture.

52. (Amended) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active <u>heteropolymeric</u> peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 3; or a salt thereof, wherein Z comprises at least two identical amino acid units.

54. (Amended) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-[20] 10 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2; or a salt thereof, [wherein Z consists of about 4 to about 10 amino acids] <u>wherein Z comprises at least two identical amino acid units</u>.

57. (Amended) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active <u>heteropolymeric</u> peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2; or a salt thereof, wherein Z comprises at least two or three Lys amino acid units.

62. (Amended) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active <u>heteropolymeric</u> peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is <u>$(Dbu)_n$ or $(Dpr)_n$, wherein n is an integer in the range from about 4 to about 10</u> [selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and

phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring]; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2; or a salt thereof [, wherein Z is $(Dbu)_n$ or $(Dpr)_n$, wherein n is an integer in the range from about 4 to about 10].

64. (Amended) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active <u>heteropolymeric</u> peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2; or a salt thereof, wherein said pharmacologically active peptide sequence (X) consists of at the most about 65 amino acid units, wherein Z comprises at least two identical amino acid units.

68. (Amended) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring [,e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid]; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with

carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2; or a salt thereof,

wherein,

Z is Lys_p-Xaa_q or Xaa_p-Lys_q, wherein p and q are integers in the range from 1 to 14, with the proviso that p+q is in the range of 3-15, and each Xaa is independently selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid and Met,

and further wherein,

X is selected from the group consisting of AF 12505 (Ile-Glu-Gly-Pro-Thr-Leu-Arg-Gln-Trp-Leu-Ala-Ala-Arg-Ala) (SEQ ID NO. 14), insulin-like growth factor I (57-70) (Ala-Leu-Leu-Glu-Thr-Tyr-Cys-Ala-Thr-Pro-Ala-Lys-Ser-Glu) (SEQ ID NO. 15), insulin-like growth factor I (30-41) (Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO. 16), insulin-like growth factor I (24-41)(Tyr-Phe-Asn-Lys-Pro-Thr-Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO. 17) , insulin-like growth factor II (33-40) (Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO. 18), insulin-like growth factor II (33-40) (Tyr-Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO. 19), insulin-like growth factor II (69-84) (Asp-Val-Ser-Thr-Pro-Pro-Thr-Val-Leu-Pro-Asp-Asn-Phe-Pro- Arg-Tyr) (SEQ ID NO. 20), growth hormone (GH)-releasing peptide-6 (GHRP-6) (His-DTrp-Ala-Trp-DPhe-Lys-NH2) (SEQ ID NO. 21), beta-Interleukin I (163-171) (Val-Gln-Gly-Glu-Glu-Ser-Asn-Asp-Lys) (SEQ ID NO. 22), beta-Interleukin II (44-56) (Ile-Leu-Asn-Gly-Ile-Asn-Asn-Tyr-Lys-Asn-Pro-Lys-Leu) (SEQ ID NO. 23), Interleukin II (60-70) (Leu-Thr-Phe-Lys-Phe-Tyr-Met-Pro-Lys-Lys-Ala) (SEQ ID NO. 24), exendin-4 (GLP-1 analog) (His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2) (SEQ ID NO. 25), exendin-3 (GLP-1 analog) (His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser) (SEQ ID NO. 26), epidermal growth factor (20-31) Cys(Acm)-Met-His-Ile-Glu-Ser-Leu-Asp-Ser-Tyr-Thr-Cys(Acm) (SEQ ID NO. 27), bivalirudin (Hirulog) (D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu) (SEQ ID NO. 28), hirulog-1 D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Tyr-Leu (SEQ ID NO. 29), C-type natriuretic peptide (1-53) (CNP) (Asp-Leu-Arg-

Val-Asp-Thr-Lys-Ser-Arg-Ala-Ala-Trp-Ala-Arg-Leu-Leu-Gln-Glu-His-Pro-Asn-Ala-Arg-Lys-Tyr-Lys-Gly-Ala-Asn-Lys-Lys-Gly-Leu-Ser-Lys-Gly-Cys-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Gly-Ser-Met-Ser-Gly-Leu-Gly-Cys; Disulfide bridge: Cys37-Cys53) (SEQ ID NO. 30), "Mini ANP" (Met-Cys-His-cyclohexylAla-Gly-Gly-Arg-Met-Asp-Arg-Ile-Ser-Cys-Tyr-Arg, disulfide bridge cys2-cys13) (SEQ ID NO. 31), Melanotan-II (MT-II, alpha-MSH4-10-NH2, or Ac-Nle4-Asp5-His6-D-Phe7-Arg8-Trp9-Lys10) (SEQ ID NO. 32), thymosin alpha1 (TA1) (Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn) (SEQ ID NO. 33), Cys-Phe-Ile-Gln-Asn-Cys-Pro-Orn-Gly-NH2, Disulfide bridge: Cys1-Cys6) (SEQ ID NO. 34), octreotide (201-995) (DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol; disulfide bridge: Cys2-Cys7) (SEQ ID NO. 35), calcitonin gene-related peptide (CGRP) (Ala-Cys-Asp-Thr-Ala-Thr-Cys-Val-Thr-His-Arg-Leu-Ala-Gly-Leu-Leu-Ser-Arg-Ser-Gly-Gly-Val-Val-Lys-Asn-Asn-Phe-Val-Pro-Thr-Asn-Val-Gly-Ser-Lys-Ala-Phe-NH_2; Disulfide bridge: Cys2-Cys7) (SEQ ID NO. 36), endomorphin-1 Tyr-Pro-Trp-Phe-NH2 (SEQ ID NO. 37); endomorphin-2 Tyr-Pro-Phe-Phe-NH_2 (SEQ ID NO. 38), nociceptin (also known as Orphanin FQ, Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln) (SEQ ID NO. 39), angiotensinogen (1-13) (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His) (SEQ ID NO. 40), adrenomodullin (1-12) (Tyr-Arg-Gln-Ser-Met-Asn-Asn-Phe-Gln-Gly-Leu-Arg) (SEQ ID NO. 41), antiarrhytmic peptide (AAP) (Gly-Pro-Hyp-Gly-Ala-Gly) (SEQ ID NO. 42), Antagonist G (Arg-DTrp-(nMe)Phe-DTrp-Leu-Met-NH_2), indolicidin (Ile-Leu-Pro-Trp-Lys-Trp-Pro-Trp-Trp-Pro-Trp-Arg-Arg-NH_2) (SEQ ID NO. 43), osteocalcin (37-49) (Gly-Phe-Gln-Glu-Ala-Tyr-Arg-Arg-Phe-Tyr-Gly-Pro-Val) (SEQ ID NO. 44), cortistatin 29 (1-13) (Glp)-Glu-Arg-Pro-Pro-Leu-Gln-Gln-Pro-Pro-His-Arg-Asp) (SEQ ID NO. 45), cortistatin 14 Pro-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Ser-Ser-Cys-Lys; Disulfide bridge: Cys2-Cys13 (SEQ ID NO. 46), PD-145065 (Ac-D-Bhg-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO. 47), PD-142893 (Ac-D-Dip-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO. 48), fibrinogen binding inhibitor peptide (His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val) (SEQ ID NO. 49), leptin (93-105) (Asn-Val-Ile-Gln-Ile-Ser-Asn-Asp-Leu-Glu-Asn-Leu-Arg) (SEQ ID NO. 50), GR 83074 (Boc-Arg-Ala-DTrp-Phe-DPro-Pro-Nle-NH_2) (SEQ ID NO. 51) Tyr-W-MIF-1 (Tyr-Pro-Trp-Gly-NH_2) (SEQ ID NO. 52), parathyroid hormone related peptide (107-111) (Thr-Arg-Ser-Ala-Trp) (SEQ ID NO. 53), angiotensinogen (1-14) Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn

(SEQ ID NO. 54), Leupeptin (Ac-Leu-Leu-Arg-CHO); or a modified [or truncated] fragment thereof; and further wherein Z comprises at least two identical amino acid units.

Claims 3, 4, 5 and 37 have been cancelled without prejudice.

Kindly add the following new claims 69-72.

69. (New) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bonded to the N terminal end of X wherein each amino acid unit in said stabilising peptide sequence, Z, is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at

about pH 7.4 at about 37°C or in serum or plasma is at least about 2; or a salt thereof, wherein Z comprises at least two identical amino acid units.

70. (New) The peptide conjugate of any one of claims 1, 52, 54, 57, 62, 64, or 68, wherein Z is further defined by having a free acid, amide or ester group.

71. (New) The peptide conjugate of claim 69, wherein Z is further defined as having a free amine or lactam group.

72. (New) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and a first sequence (Z)and a second sequence (Z),

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein the first sequence (Z) and the second sequence (Z) are each a stabilising peptide sequence of 4-20 amino acid units in which the first sequence (Z) is covalently bonded to the N terminal end of X and the second sequence (Z) is covalently bonded to the C terminal end of X, wherein each amino acid unit in the first and second peptide sequence (Z) are independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2; or a salt thereof, wherein each of the first sequence (Z) and the second sequence (Z) comprises at least two identical amino acid units.

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